International Journal of Infectious Diseases (2006) 10(S1) 46–51

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Abstracts

Innate Immunity and Sepsis

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Macrophage Migration Inhibitory Factor (MIF) Gene Polymorphisms and Tuberculosis

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Background: The pro-inflammatory cytokine MIF is an important effector molecule of innate immunity and inflammation. Two functional polymorphisms of the MIF promoter, a 5 to 8 CATT tetranucleotide repeat at -794 (-794 CATT5–8) and a G/C single nucleotide polymorphism at -173 (-173*G/C SNP), have been associated with susceptibility to and/or severity of rheumatoid arthritis, atopy, colitis and erythema nodosum in sarcoidosis. Circulating MIF levels are elevated in patients with tuberculosis. Moreover, MIF has been shown to restrict the intracellular growth of virulent *Mycobacterium tuberculosis* in macrophages.
Objective: To study whether MIF gene polymorphisms were associated with susceptibility to or severity of *tuberculosis* (TB) and to analyse the functional and biological effects of MIF polymorphisms in vitro. Methods: Case control study including healthy Mantoux positive adults, healthy Mantoux positive and negative children and children with active TB from 2 South African populations: the Xhosa (black) and the Cape coloured (descendants from a mixed population of imported slaves). -794 CATT5–8 microsatellite and -173*G/C SNP were detected by high-resolution gel-electrophoresis and TaqMan® SNP Genotyping Assay, respectively. The most frequently occurring MIF promoter (-1073/+129) alleles were cloned into a luciferase reporter vector and transfected into human THP-1 monocytic cells.
Results: The frequency of the CATT6–6 genotype was decreased in Xhosa and Cape coloured TB patients. Furthermore, the -794 CATT6–6 genotype was reduced in Cape Coloured with extrapulmonary TB. In vitro experiments revealed an increased MIF CATT6-promoter transcriptional activity in resting THP-1. There was no association between the -173*G/C SNP and the susceptibility or severity of tuberculosis.
Conclusions: We observed reduced CATT6 allele and genotype frequencies in Xhosa and Cape Colored TB patients and an increased MIF CATT6-promoter transcriptional activity in vitro. We postulate that carriers of the MIF CATT6 allele may have higher MIF levels which may help to contain *Mycobacterium tuberculosis* growth, resulting in improved host defense against *Mycobacterium tuberculosis*.

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Macrophage Migration Inhibitory Factor Plays an Important Role in the Host Innate Immune Defenses against *Candida* Infection

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Background: Invasive candidiasis has emerged worldwide as an increasingly frequent cause of opportunistic infections in critically ill and immunocompromised patients that are associated with high morbidity and mortality. The balance between pro-inflammatory (IFNγ and IL-12) and anti-inflammatory (IL-10) cytokines is a key determinant of the outcome of *Candida* infections. Macrophage migration inhibitory factor (MIF), a pro-inflammatory cytokine, is an important effector molecule of innate immunity and has been shown to play a central role in the pathogenesis of bacterial sepsis.
Objective: To study the role of MIF in the pathogenesis of invasive candidiasis.
Methods: BALB/c mice were injected with anti-MIF or control IgG antibodies (2 mg i.p/mouse) 30 minutes before an I.V. injection of $3.5–5\times10^5$ CFU of a clinical isolate of *C. albicans*. MIF, IFNγ, IL-12 and IL-10 levels and fungal loads were measured in blood, spleen and kidney 1, 2, 3, 5 and 9 days post-infection. Body weight and survival were followed daily.
Results: After intravenous injection, *C. albicans* was rapidly cleared from the circulation and pref-